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CARDIOMETABOLIC RISK OF SECOND-GENERATION ANTIPSYCHOTIC MEDICATIONS DURING FIRST-TIME USE IN CHILDREN AND ADOLESCENTS

INTRODUCTION

Atypical antipsychotic prescribing for children is on the rise. These medications are being used first-line in conditions such as bipolar disorder, psychotic disorders and nonpsychotic mental disorders. Most healthcare providers are aware of the cardiometabolic side effects that are associated with this class of medicine. Lipid changes, glucose abnormalities, and weight gain are a few of the adverse effects. These side effects are of great concern in a pediatric population which is still developing because they are predictive factors of adult obesity, the metabolic syndrome, cardiovascular morbidity and malignancy. Recently there have been studies which have indicated that the pediatric population is more sensitive to weight gain associated with antipsychotics. In addition, a few limited studies have suggested that there are little to no metabolic effects of these drugs on pediatric patients. The problem with this emerging data is the incidence of prior exposure in the patients to antipsychotic medication and the effects that prior exposure can have on the cardiometabolic effects. In order to evaluate the true effect of these medications on the pediatric population, studies must be completed in patients who have not been previously exposed to antipsychotics.

Corresponding author Christoph U. Correll, MD of the Zucker Hillside Hospital Psychiatry Research along with others conducted a prospective study in a large cohort of pediatric patients who had no prior exposure to antipsychotic medications. The objective of the study was to assess the cardiometabolic side effects of aripiprazole, olanzapine, quetiapine, and risperidone in treatment

naïve pediatric patients. The authors hypothesized that after 12 weeks of treatment there would be significant negative changes in body composition and metabolic parameters.

METHODS

Between December 2001 and September 2007, patients were recruited from inpatient and outpatient pediatric clinics to take part in the non-randomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study. This was a cohort study of antipsychotics in pediatric psychotic, mood, or aggressive spectrum disorders. Data regarding cardiometabolic effects due to antipsychotics was collected as part of this study. All patients or caregivers signed informed consent. The North Shore-Long Island Jewish Health System was the Institutional Review Board (IRB) and approved the study.

Inclusion and exclusion criteria are listed in the table:

Inclusion Criteria	Exclusion Criteria
• Age 4-19 years. • ≤7 days of lifetime antipsychotic treatment. • Psychiatric illness requiring antipsychotic medication initiation. • Consent or baseline anthropometric and biochemical assessments within 7 days of antipsychotic medication initiation.	• Treatment with ≥1 antipsychotic medication. • History of a past eating disorder or a current eating disorder. • Thyroid dysfunction determined through biochemical evidence. • Acute medical disorders. • Pregnancy or breastfeeding. • Wards of the state. • Leaving the catchment area within 4 weeks.

Diagnosis of psychiatric disorders, past treatment history, and postpubertal status were determined through chart assessment and interviews of clinicians, patients and/or caregivers. Race and ethnicity information was also obtained due to the possibility of these factors playing a role in cardiometabolic outcomes. Clinicians chose the antipsychotic most appropriate for the patient as well as the dose, other medications, and changes in treatment.

The primary outcome was absolute and relative change in weight. There were several secondary outcomes. The first was a change in body composition parameters including body mass index (BMI), BMI percentiles and z scores, fat mass and waist circumference. The second was a change in fasting metabolic parameters including total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), ratio of HDL to TG, glucose and insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR). Other secondary outcomes were incidence rates of weight gain ≥7%, individual metabolic parameters, dyslipidemia, and the metabolic syndrome.

Assessment of the patients occurred at baseline and at 4, 8, and 12 weeks. The assessment was done after the patients had fasted overnight for at lease eight hours. The following table shows how the patients were assessed:

Parameters	Assessment
Height	• Measured 3 times • Used the Seca 214 stadiometer
Weight	• Impedantiometry with the Tanita Body Composition Analyzer TBF-310 • Weighed with clothes on, empty pockets, no shoes, no socks o Patients >150cm ▪ -1.3kg: long trousers and long sleeved shirt or sweatshirt ▪ -1.1kg : short sleeves and 1 of the 2 items listed above ▪ -0.7kg: short pants or short-sleeve or light shirts ▪ -0.5kg: underwear alone o Patients <150cm but >120cm: ▪ Subtract 0.2kg from formula o Patients <120cm: ▪ Subtract 0.45kg from the formula
BMI	• Impedantiometry with the Tanita Body Composition Analyzer TBF-310
Fat Mass	• Impedantiometry with the Tanita Body Composition Analyzer TBF-310
Waist Circumference	• Measures at the superior iliac crest and umbilicus • Used largest point of abdominal circumference
Fasting Blood	• Drawn 7am-11am prior to taking medications • Obtained at each postbaseline visit • Reminded to fast overnight before each visit • Questioned about compliance to fasting o Rescheduled if patient did not fast o Blood work repeated if glucose ≥100mg/dL or if insulin increased >100% from last assessment • Glucose levels analyzed with the Roche Hitachi 747 chemistry analyzer • Insulin levels analyzed by the Roche Elecsys 2010 immunochemistry analyzer
Lipids	• Analyzed with the Roche Hitachi 747 chemistry analyzer
Insulin Resistance	• The homeostasis model assessment of insulin resistance (HOMA-IR) • A value of >4.39 was diagnostic for insulin resistance

STATISTICS

Intent to treat was based on patients who had one or more postbaseline assessments and a web-based calculator was used to calculate BMI z scores adjusted for sex and age.

Statistical tests used were the chi-squared test, Fisher exact tests (for categorical variables) and the Kruskal-Wallis test (for continuous variables) for comparison of baseline characteristics of the

groups. Mixed-models repeated-measures analysis of variance was used to determine the change in continuous variables within each group. The repeated factor was time relative to baseline at 4, 8, and 12 weeks and the summary statistics were shown as adjusted least-squares means and 95% confidence intervals. Last-observation-carried-forward analysis was used for incidence rates of outcomes which were divided (pubertal status and dose). The Pearson chi squared test was used to control for baseline variables which were significantly different.

Post hoc analysis was performed on change in weight as well as BMI z scores due to the large difference which was found in the study. Imputation was applied to the endpoint continuous variables and categorical outcomes to confirm that the mixed-models repeated-measures analysis of variance and last-observation-carried-forward analysis results were not biased. There was no difference in analysis with imputation and analysis without imputation. Patients taking co-medications which affected weight as well as co-medication that did not affect weight had repeat analysis performed. Pubertal status and dose effect were explored through additional analysis through division of the data into two groups. Analysis was completed with SAS® statistical software and were 2-sided with an alpha level of <0.5.

A paired *t* test was used to determine generic power analysis for a mean change from baseline to the end of 12 weeks per one standard deviation. Except for the comparison group, the study was powered at 80% to show significant differences. The effect size of each group was as follows: 0.43 for olanzapine, 0.45 for aripiprazole, 0.48 for quetiapine, and 0.24 for risperidone. The comparison group had an effect size of 0.78.

RESULTS

A total of 338 patients were enrolled in the study. Out of an original 505 treatment naïve patients recruited, 76 declined, 44 were unable to be contacted or enrolled within one week, 18 had an eating disorder, 18 were wards of the state, 7 had medical reasons to be excluded and 4 were expected to be transferred out of the catchment area in less then 4 weeks. Out of the 338 patients who were enrolled after the exclusions, 6 were prescribed ziprasidone and 60 did not receive any postbaseline assessments. As a result a total of 272 patients were analyzed.

A comparison group was comprised of patients who refused or stopped taking the medication within 4 weeks but had the 8 or 12 week assessment. This group contained 15 patients who were analyzed and the average exposure to an antipsychotic was 12.4 days. C

Changes in body composition results are as follows:

- Weight increased (95% confidence interval [CI]):
  - 8.5kg with olanzapine ($p<0.001$)
  - 6.1kg with quetiapine($p<0.001$)
  - 5.3kg with risperidone($p<0.001$)
  - 4.4kg with aripiprazole($p<0.001$)
  - 0.2kg in the comparison group ($p=0.77$)

- Fat Mass increased (95% CI):
  - 4.12kg with olanzapine ($p<0.001$)
  - 2.82 kg with quetiapine($p<0.001$)
  - 2.45kg with risperidone($p<0.001$)
  - 2.43kg with aripiprazole($p<0.001$)
  - 0.35 kg in the comparison group ($p=0.39$)

- Waist Circumference increased(95% CI):
  - 8.55cm with olanzapine ($p<0.001$)
  - 5.27cm with quetiapine($p<0.001$)
  - 5.10cm with risperidone($p<0.001$)
  - 5.40cm with aripiprazole($p=0.001$)
  - 0.70cm in the comparison group ($p=0.40$)

Each antipsychotic medication was also associated with shifts to overweight or obese status. As far as changes in metabolic parameters over time, olanzapine was associated with statistically significant negative effects on glucose and insulin levels, insulin resistance, ratio of TG to HDL, total cholesterol, LDL, TG and non-HDL cholesterol. Quetiapine significantly changed total cholesterol, TG, non-HDL cholesterol and ratio of TG to HDL. Risperidone caused a significant rise in TG and ratio of TG to HDL. Aripiprazole was not associated with any significant changes in metabolic parameters. In regards to other metabolic parameters, quetiapine was associated with moderate incidence of hyperglycemia and olanzapine was associated with the highest incidence of hyperglycemia. Pubertal status did not have any effect on the metabolic changes which took place within the groups.

Risperidone doses above 1.5mg/d caused more changes in weight, waist circumference, fat mass, BMI z scores, total cholesterol and non-HDL cholesterol. Patients receiving greater doses of olanzapine >10mg/d also experienced greater increases in total cholesterol and non-HDL cholesterol.

AUTHORS CONCLUSIONS

The authors concluded the antipsychotics studied are all associated with changes in body composition parameters, especially weight gain. Negative effects on metabolic parameters were less consistent. Increased fat mass, increased waist circumference, and abnormal weight in children are associated with negative cardiovascular outcomes as adults, therefore, the results of this study should cause concern in healthcare providers.

The study has also indicated a possible new theory as to why children gain weight from atypical antipsychotics. It appears children gain more weight because they have less lifetime exposure to antipsychotics compared to most adults. For instance, the weight gain in this study was greater then the weight gain in adults with chronic schizophrenia as well as adults with first-episode schizophrenia (in the latter sample 24% of adults were naïve to antipsychotic treatment). In comparison to other pediatric studies such as a study on pediatric schizophrenia and bipolar disorder and another study comparing olanzapine and risperidone (only 36% and 33% respectively naïve to

antipsychotic treatment) this current study had more weight gain. The findings on absolute and relative weight gain were also similar to a 3-month adolescent trial on quetiapine where 77% of patients were antipsychotic naïve. In addition, the results were similar to a 3 month adult study on first episode schizophrenia where 100% of the adult patients were antipsychotic naïve and a 4 month study where 91% of patients had less then one week exposure to antipsychotic medications. The similar results despite the differences in age groups with these studies suggest that age and development differences may not be as important factors in the mechanism of weight gain but prior exposure to these medications could be.

Olanzapine had the greatest negative impact on all metabolic parameters. Quetiapine affected several lipid parameters and risperidone increased TG. Aripiprazole was only associated with a near significant increased in LDL. Lower effect sizes of aripiprazole could have caused the lack of change on other metabolic parameters. A type II error due to a small sample size could have also occurred and affected the lipid parameters. Lack of significant changes in glucose levels with quetiapine and risperidone could also be attributed to a small effect size.

The authors have suggested that further research should be done on the factors of weight gain and BMI in regards to metabolic abnormalities. They also suggest a longer study is needed to better understand the trend of metabolic changes with the use of second-generation antipsychotics. More research should also be done to determine when and how often diabetes or the metabolic syndrome occur as well as the reason for the delay in developing insulin resistance and metabolic syndrome in children with rapid weight gain.

The data from the study showed higher doses of olanzapine (>10mg/d) were associated with greater metabolic changes. Body composition changes were only shown to be dose related with risperidone. This data could support a theory that metabolic changes with olanzapine are independent of weight changes. More studies should be done to specifically examine dose-relationship on metabolic and body composition changes.

The authors suggest that guidelines for antipsychotic use in naïve pediatrics should include monitoring cardiometabolic effects after the first three month of treatment. The use of atypical antipsychotics should be considered after weighing risks and benefits. Healthcare providers should consider indication for use and alternatives with lower risks before prescribing these drugs. Healthcare providers should also be prudent on monitoring and managing adverse effects.

AUTHORS LIMITATIONS

Limitations are as listed:

- Study was nonrandomized and of observational design.
- Baseline differences hindering stringent group comparisons.
- Flexible dosing of medications and short treatment duration.
- Allowance of co-medications.
- Small comparison group and lack of first-generation antipsychotic.

CRITIQUE

Dr. Correll, Dr. Manu, Dr. Kane and Dr. Malhotra were all reported to be consultants, have received honoraria or participated as members of the speaker's bureau for multiple pharmaceutical companies including those which manufacturer the drugs being studied. This was disclosed in financial disclosures however it opens up a possibility for conflicts of interest.

The introduction did not give a detailed review of the disease states which these medications were being studied in. Diagnostic criteria for the disease states were not explicit. Determination of diagnosis and previous treatment was done by chart review, discussion with the treatment clinician and interviews of the patient and caregiver.

Allocation to the different treatment groups was not random. Clinicians could prescribe which drug they felt was suitable for the patient. They also had the ability to determine dose and change treatment as they saw fit. There were no rules as to how dosages should have been adjusted.

Some of the baseline characteristics between groups had differences which were statistically significant. The results section did not discuss the differences in baseline characteristics or how they were accounted for. The methods section stated that the Pearson chi-squared test was used to control for significantly different baseline values.

The comparison group was small and was not receiving standard care. The changes which took place in the comparison group were not statistically significant. The results should be looked at skeptically when contrasting to the comparison group.

The study may not have been long enough to see changes in some of the parameters. The results were reported after a median of 10.8 week but treatment was continued until 12 weeks.

REFERENCES

Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents. JAMA 2009 Oct. 28; 302 (16): 1765-73.